Neurochemistry International 124 (2019) 10–18

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/neuint

# Expression of immediate early genes in brain reward circuitries: Differential regulation by psychostimulant and opioid drugs

Veronica Bisagno[a], Jean Lud Cadet[b,*]

[a] Instituto de Investigaciones Farmacológicas (ININFA-UBA-CONICET), Junín 956, piso 5, C1113, Buenos Aires, Argentina
[b] NIDA Intramural Program, Molecular Neuropsychiatry Research Branch, 251 Bayview Boulevard, Baltimore, MD, 21224, USA

ARTICLE INFO

*Keywords:*
Immediate early genes (IEGs)
Psychostimulant
Opioid

ABSTRACT

Although some of the clinical manifestations of substance use disorders might be superficially similar, it is highly likely that different classes of abused drugs including opioids (heroin, morphine, and oxycodone, other opioids) and psychostimulants (cocaine and amphetamines) cause different neuroadaptations in various brain regions dependent in the distribution and concentration of their biochemical sites of actions. In fact, different molecular networks are indeed impacted by acute and chronic administration of addictive substances. Some of the genes whose expression is influenced by the administration of these substances are immediate-early genes (IEGs). IEGs include classes of low expression genes that can become very highly induced within seconds or minutes of activation by endogenous or exogenous stimuli. These IEGs might play important roles in activating target genes that regulate adaptations implicated in the behavioral manifestations diagnosed as addiction. Therefore, the purpose of this review is to provide an overview of recent data on the effects of psychostimulants and opioids on IEG expression in the brain. The review documents some contrasting effects of these classes of drugs on gene expression and indicates that further studies are necessary to identify the specific effects of each drug class when trying to predict clinical responses to therapeutic agents.

## 1. Introduction

Drug addiction is defined as a chronic relapsing brain disease that is associated with diverse clinical presentations including neurological and psychiatric signs and symptoms (Cadet and Bisagno, 2016). These clinical manifestations of substance use disorders (SUDs) are probably secondary to plastic epigenetic, transcriptional, and functional adaptations in brain regions that subsume reward and non-reward pathways in the brain (Cadet et al., 2014). Although some of the clinical manifestations of SUDs might be superficially similar, it is likely that different classes of abused drugs including opioids (heroin, morphine, and oxycodone, other opioids) and psychostimulants (cocaine and amphetamines) (Hedegaard et al., 2017) may cause different neuroadaptations in various brain regions dependent in the distribution and concentration of their biochemical sites of actions. For example, psychostimulants interact primarily with monoaminergic transporters including those for dopamine (DA), norepinephrine (NE), and serotonin (5-HT) (Amara and Sonders, 1998) whereas opioids stimulate opioid receptors (Kreek et al., 2012).

Mesocortical circuitries that subserve basic and critical biological functions including decision-making, goal-oriented behaviors, and motor outputs related to reward is thought to potentially mediate the addictive properties of addictive drugs (Koob and Volkow, 2016). DA neurons project from the ventral tegmental area (VTA) to the prefrontal cortex (PFC), the ventral striatum or nucleus accumbens, (NAc), as well as to the hippocampus, amygdala, and other forebrain regions (Koob and Volkow, 2010). DA neurons from the substantia nigra pars compacta (SNpc) that project to the dorsal striatum, which is an important structure in habit forming, appears to also be involved in regulating compulsive drug taking over the longterm (Wise, 2004). Therefore, a better understanding of the ways that the connections between these various brain regions weaken or strengthen during the clinical course of escalating drug taking may help to identify sub-groups of addicted patients and/or predict responses to various treatment approaches. This understanding may also depend on the elucidation of molecular networks that are impacted by acute and chronic administration of addictive substances (Cadet et al., 2016). Some of the genes impacted by the administration of various substances of abuse are immediate-early genes (IEGs) (Robison and Nestler, 2011). IEGs are low expression genes that can become very highly expressed within seconds or minutes

* Corresponding author. Molecular Neuropsychiatry Research Branch Intramural Research Program, NIDA/NIH/DHHS, 251 Bayview Boulevard Baltimore, MD, 21224, USA.
*E-mail address:* jcadet@intra.nida.nih.gov (J.L. Cadet).

https://doi.org/10.1016/j.neuint.2018.12.004
Received 1 October 2018; Received in revised form 27 November 2018; Accepted 13 December 2018
Available online 14 December 2018
0197-0186/ Published by Elsevier Ltd.

**Abbreviations**

| | |
|---|---|
| 5-HT | serotonin |
| AMPA | α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid |
| Arc | activity-regulated cytoskeleton-associated protein |
| bHLH | basic helix-loop-helix |
| CaM | calmodulin |
| CaMKIV | calmodulin-dependent protein kinase IV |
| c-Jun | jun proto-oncogene |
| CNS | central nervous system |
| CREB | cAMP response element binding protein |
| CREM | cAMP-responsive element modulator gene |
| DA | dopamine |
| DAT | dopamine transporter |
| dlPFC | dorsal Prefrontal Cortex |
| Egr | early growth response gene |
| ERK | extracellular signal-regulated kinase |
| FOS; c-Fos | Finkel–Biskis–Jinkins murine osteosarcoma viral oncogene |
| Fra2 | Fos-related antigen 2 |
| GWAS | genome-wide association studies |
| HDAC | histone deacetylase |
| IEGs | immediate-early genes |
| METH | methamphetamine |
| MKP-1 | mitogen-activated protein kinase phosphatase 1 |
| MOP-r: | Mu Opioid Receptor |
| mPFC | medial Prefrontal Cortex |
| MSK | mitogen and stress-activated kinase |
| MW | morphine withdrawal |
| NAc | nucleus accumbens |
| NE | norepinephrine |
| NET | norepinephrine transporter |
| NMDA | N-methyl-D-aspartate |
| Npas4 | neuronal PAS domain protein 4 |
| NPTX1 | neuronal pentraxin-1. Gene |
| NR4A | nuclear receptor 4A |
| PFC | prefrontal cortex |
| PKA | protein kinase A |
| PKC | protein kinase C |
| ROS | reactive oxygen species |
| RSK | ribosomal S6 kinase |
| SA | self-administration |
| SERT | serotonin transporter |
| SNpc | substantia nigra pars compacta |
| SUDs | substance use disorders |
| TFs | transcription factors |
| TSSs | transcription start sites |
| VGCC | voltage-gated calcium channel |
| VTA | ventral tegmental area |

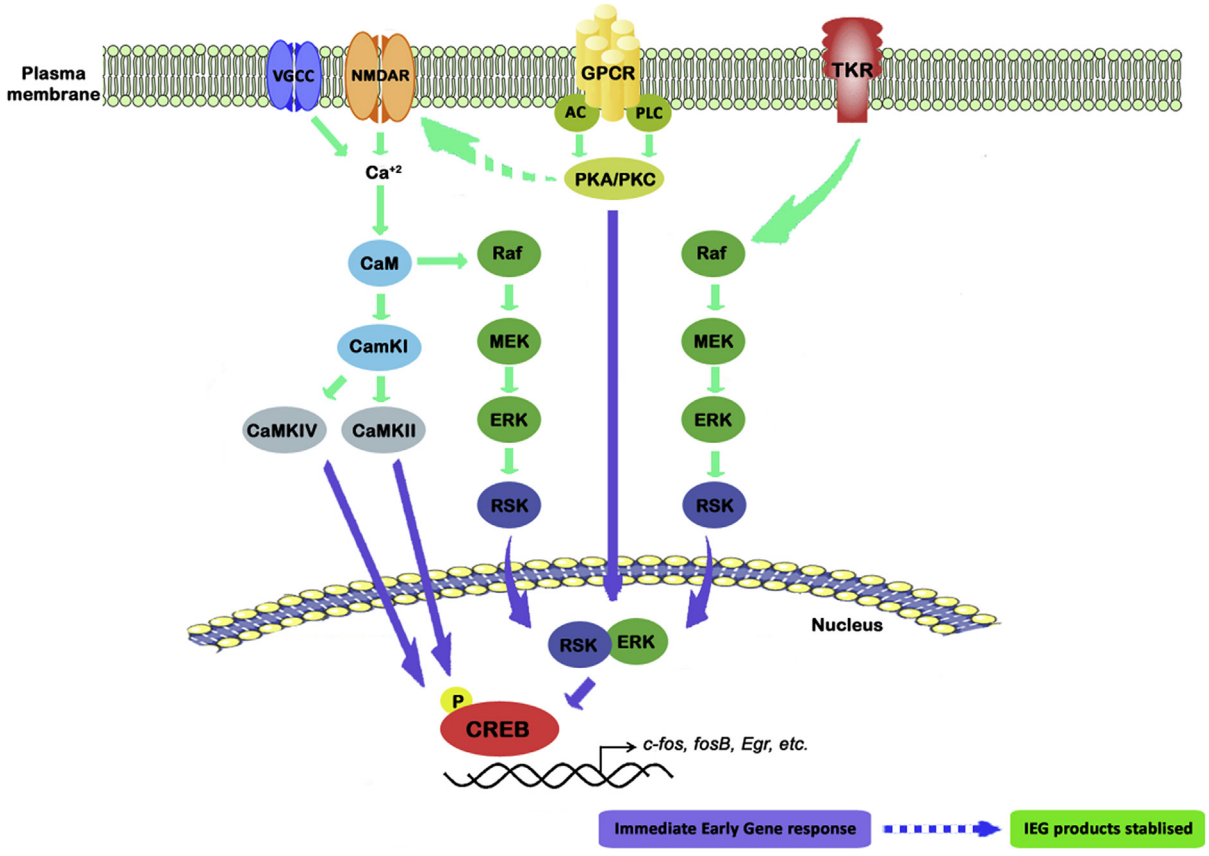


**Fig. 1.** Overview of signaling pathways that results in neuroplastic changes induced by drug intake and neuronal activity via $Ca^{2+}$ (via NMDAR or VGCC), GPCR or TKR. Distinct but overlapping pathways concur on the activation of the CREB signaling pathway via CREB phosphorylation (pCREB). Early increases in IEG expression are dependent, in part, on pCREB which appears to be a common hub of many extracellular stimuli. Abbreviations: Protein kinase A or C (PKA/PKC), Calmodulin (CaM), calmodulin-dependent protein kinase IV (CaMKIV), extracellular signal-regulated kinase (ERK), ribosomal S6 kinase (RSK), and mitogen and stress-activated kinase (MSK).

**Table 1**
Acute drug-induced changes in IEG expression in striatal tissues after acute drug exposure. Opioids include heroin or morphine administration.

| | Cocaine | Methamphetamine | MDMA | Opioids |
|---|---|---|---|---|
| **c-Fos** | ↑ [Graybiel et al., 1990; Hope, 1992 (NAc); Piechota et al., 2010] | ↑ [Graybiel et al., 1990; Gross and Marchall, 2009; Hirata et al., 1998, Thiriet et al., 2001 (NAc); Tomita et al., 2013; Beauvais et al., 2010; Piechota et al., 2010; McCoy et al., 2011; Martin et al., 2012 (NAc)]<br>↑ [Only in c-Fos + neurons, [Liu et al., 2014] | ↑ [Erdtmann-Vourliotis et al., 1999; Salzmann et al., 2003 (NAc); Hargreaves et al., 2007 (NAc); Benturquia et al., 2008] | ↑ [Liu et al., 1994; Bontempi and Sharp, 1997; Steffensen et al., 2006; Ziółkowska et al., 2012]<br>↑**Delayed (4 h s post injection)** [Piechota et al., 2010] |
| **FosB** | ↑ [Hope, 1992 (NAc); Nye and Nestler, 1996; Chen et al., 1995, 1997; Zhang et al., 2002, Larson et al., 2010]<br>↑ Only in c-Fos + neurons, [Guez-Barber et al., 2011] | ↑ [McCoy et al., 2011; Martin et al., 2012 (NAc)]<br>↑ **Delayed (4 h s post injection),** [Beauvais et al., 2010, Torres et al., 2015 (NAc)]<br>↑Only in c-Fos + neurons, [Liu et al., 2014] | ↑ [Benturquia et al., 2008] | ↑ [Muller and Unterwald, 2005] |
| **Jun family** | ↑ [Hope, 1992 (NAc)] | ↑ [Beauvais et al., 2010; McCoy et al., 2011; Martin et al., 2012 (NAc); Torres et al., 2015 (NAc)] | | ↑ [Liu et al., 1994] |
| **Fra** | ↑ [Zhang et al., 2002] | ↑ [Pennypacker et al., 2000; McCoy et al., 2011; Torres et al., 2015 (NAc); Beauvais et al., 2010; Torres et al., 2015 (NAc)] | ↑ [Pennypacker et al., 2000] | ↑ [Ziółkowska et al., 2012] |
| **Egr family** | ↑ [Hope, 1992 (NAc)] | ↑ [Hirata et al., 1998; McCoy et al., 2011]<br>↑ **Delayed (2-4 h s post injection)** [Beauvais et al., 2010, Torres et al., 2015 (NAc); Thiriet et al., 2001 (NAc)] | ↑ [Shirayama et al., 2000; Benturquia et al., 2008] | ↑ [El Rawas et al., 2009]<br>↑ **Delayed (4 h s post injection)** [Ziółkowska et al., 2015] |
| **Arc** | ↑ Only in c-Fos + neurons, [Guez-Barber et al., 2011] | ↑ [Beauvais et al., 2010]<br>↑Only in c-Fos + neurons, Liu et al., 2014] | ↑ [Beveridge et al., 2004] | ↑ **Delayed (4 h s post injection)** [Ziółkowska et al., 2012, 2015] |
| **Npas4** | ↑ [Piechota et al., 2010] | ↑ [Martin et al., 2012 (NAc)]<br>↓ **Delayed (24 h s post injection)** [Martin et al., 2012 (NAc)] | ↑ [Piechota et al., 2010] | ↑ [Piechota et al., 2010] |

of endogenous or exogenous stimuli (Leslie and Nedivi, 2011). Therefore, the purpose of this paper is to provide an overview of recent data on the effects of psychostimulants and opioids on IEG expression in the brain. Whenever possible, we will also compare and contrast the impact of these two classes of drug on IEG expression.

Psychostimulants directly affect DA transmission by elevating extracellular DA and prolonging DA receptor signaling. Cocaine and amphetamines respectively act by diverse mechanisms as inhibitors of monoamine transporters (DAT, NET, SERT) (Kuhar et al., 1991) or promotes DAT-mediated reverse-transport of DA into the synaptic cleft (Sulzer et al., 1995). By contrast, heroin, morphine, and other prescription opioids including oxycodone or hydrocodone (OxyContin and Vicodin, respectively) act primarily as agonists at mu opioid receptors (Kreek et al., 2012). Stimulation of endogenous opioid receptors reduces GABA released at synapses in the brain (Vaughan et al., 1997). Because GABA is a known inhibitor of DA release, the end results of the actions of these drugs are increased DA in the NAc (Leone et al., 1991) and the caudate-putamen (Chesselet et al., 1981).

In addition to their effects on monoaminergic systems, psychostimulants can also impact brain opioid systems (Kreek et al., 2012). Cocaine alters brain mu opioid receptors (Unterwald et al., 1994; Zubieta et al., 1996). Recently it has been reported that compulsive methamphetamine self-administering rats show increased expression of proenkephalin and prodynorphin mRNAs in the NAc in comparison to control and abstinent rats suggesting a role of opioid neuropeptides in the manifestation of methamphetamine addiction (Cadet et al., 2016).

Although there are reports of self-administration protocols for heroin (Wade et al., 2015) and oxycodone (Wade et al., 2015; Blackwood et al., 2018), there is some evidence from preclinical studies showing that rodents appear to respond differentially to access to psychostimulants and opioids (Badiani et al., 2011). For example, prior exposure to social stress promotes escalation of cocaine self-administration but not heroin self-administration (Cruz et al., 2011). Of note, dopaminergic systems appear to be differentially involved in stimulant and opioid self-administration by rodents. Specifically, DA receptor blockade or lesions of the mesolimbic DA system decrease cocaine but not heroin self-administration (Pettit et al., 1984). Lastly, trait impulsivity predicts escalation of cocaine intake (Dalley et al., 2007) but not heroin intake (McNamara et al., 2010).

### *1.1. IEGs and their regulation*

Before delving into the regulation of IEGs by substances of abuse, we will provide a very brief synopsis of the general regulation of some IEGs. As mentioned earlier, IEGs encode inducible transcription factors: e.g. c-Fos, c-Jun, JunB, Egr, Nr4a etc.) that can interact with promoter regulatory elements of downstream effector genes to regulate their expression (see Fig. 1). Thus, IEGs can influence waves of transcriptional activities based on the genes whose activities they might have stimulated or inhibited (Bahrami and Drabløs, 2016). Because gene transcription is also regulated by epigenetic phenomena that include chromatin modifications, post-translational histone alterations, and changes in the binding of transcription factors (TFs) at gene promoters (Godino et al., 2015), it is also likely that IEGs can impact epigenetic phenomena at various molecular levels (Bahrami and Drabløs, 2016). For example, it has been shown that repressed intergenic and intragenic transcription start sites (TSSs) enriched with active chromatin marks and RNA polymerase II are strongly associated with the presence of IEGs (Rye et al., 2014). Thus, drugs of abuse that influence IEG expression may cause substantial epigenetic consequences in the brain.

### *1.2. Regulation of IEGs by cocaine, methamphetamine and 3,4-Methylenedioxymethamphetamine*

#### *1.2.1. Cocaine*

Cocaine produces its psychoactive effects by acting on the brain's

mesocorticolimbic monoaminergic systems. Cocaine binds to DA, serotonin, and norepinephrine transport proteins (DAT, SERT, and NET respectively) and prevents re-uptake of these monoamines into pre-synaptic neurons (Kristensen et al., 2011; Kuhar et al., 1991). DAT, but not the SERT, appears to be critical in mediating the reinforcing effects of cocaine. Mice lacking the DAT failed to acquire and maintain cocaine self-administration but the deletion of the SERT did not induce this effect (Thomsen et al., 2009).

Several groups of investigators have also studied the effects of acute and chronic cocaine administration of the expression of several IEGs in the brain, see Table 1 and Table 2. For example, acute injection of cocaine can cause substantial increases in c-Fos expression in the NAc (Hope et al., 1992). Acute cocaine (1 h post injection) also increases c-Jun, FosB, JunB, and Egr1 expression in that structure (Hope, 1992). The neuronal PAS domain protein 4 (Npas4) is also responsive to acute cocaine administration in the striatum (Piechota et al., 2010). Importantly chronic pre-administration of cocaine resulted in the suppression of the acute effects of cocaine on c-Fos expression (Hope et al., 1992). These observations suggest that chronic exposure to cocaine may have impacted epigenetic mechanisms that regulate acute cocaine's effects on c-Fos expression.

Another gene of interest is FosB. Chronic administration of cocaine led to the accumulation of a protein that was identified using Western blot analysis (Hope et al., 1994). The FosB message suffers splicing that results in different proteins such as the full-length FosB (50 kDa) and a stable truncated splice variant of the FosB gene named ΔFosB (35–37 kDa) (Hope et al., 1994; Chen et al., 1995, 1997). These changes may be related to the effects of chronic cocaine on the accumulation of CREB-binding protein onto the FosB promoter (Levine et al., 2005). Changes in ΔFosB have been shown to be involved in several behavioral effects of cocaine including behavioral sensitivity (Nestler et al., 2001). Accordingly, Nestler et al. (2001) have suggested that ΔFosB isoforms may act as a "molecular switch" to facilitate the transition from measured drug use to compulsive drug taking behaviors. It needs to be noted, nevertheless, that cocaine exposure can increase ΔFosB in striatal tissues, whether given passively or under self-administration situations (Larson et al., 2010), suggesting the need for further evaluation of the role of that protein in conditions that are contingently or non-contingently determined since an addiction diagnosis involves self-administration of drugs not just passively administered drugs.

The rate at which cocaine is delivered influences its acute psychological and physiological effects in humans (Nelson et al., 2006). Similarly, rapid cocaine infusions potentiate its ability to induce c-Fos and Arc mRNA levels in the brain (Samaha et al., 2004). Nevertheless, it has not yet been determined systematically how the rapidity of cocaine distribution within the brain after intranasal, smoking, and intravenous routes actually influences the developmental course of addiction.

Drugs of abuse can cause adaptations in mesocortical DA signaling that lead to addiction-induced changes in cortical and subcortical processing, particularly on PFC function. (Cadet and Bisagno, 2013). Abnormalities have been identified in frontal networks that subsume poor self-regulation and the loss of control over drug-seeking behavior in cocaine-dependent patients (Goldstein and Volkow, 2011). The main effect of cocaine on the PFC is to increase PFC activity, as measured by neuroimaging studies (Goldstein and Volkow, 2011). As the length of access to the drug and drug expectation modulate PFC activity, increases in activity that occur during drug administration may be indicative of neuroadaptations (Goldstein and Volkow, 2011). Changes in IEG expression appear to be a major component of cocaine-induced plasticity in the PFC. Indeed, presentation of response-contingent cocaine-paired cues during reinstatement induced a widespread pattern of c-Fos expression throughout the brain, including several prefrontal cortical, limbic, and striatal subregions (Kufahl et al., 2009).

Gao et al. (2017) compared the effects of 10 and 60-day self-administration of cocaine on the expression of several IEGs in medial PFC (mPFC) and striatal tissues. Cocaine SA increased expression of 6 IEGs in the dorsal and ventral striatum. These include c-Fos, FosB/ΔFosB, Egr2, Egr4, and Arc. In the mPFC, there was one additional gene that was impacted by cocaine SA, namely Homer1 (Gao et al., 2017). Importantly, there were no major differences between patterns of IEG expression after 10 or 60 days of cocaine self-administration, except for FosB/ΔFosB in the dorsal striatum and Egr2 in the mPFC (Gao et al., 2007). Egr2 in mPFC was greatly induced following long-term (60 days) compared with short-term (10 days) exposure suggesting that Egr2 up-regulation might be related to cognitive control over drug seeking (Gao et al., 2007). The opposite trend was found for the striatal expression of FosB/ΔFosB, FosB/ΔFosB, and a smaller magnitude was seen after cocaine extended exposure compared with short-term (Gao et al., 2007).

Potential roles of Npas4 in cocaine-mediated adaptations were reported by Ye et al. (2016). Npas4 is a member of the basic helix-loop-helix (bHLH) transcription factor family that is almost exclusively expressed in the brain. Additionally, Npas4 is unique in that it is mainly activated by neuronal activity (Sun and Lin, 2016). The adult brain show low levels of Npas4 expression, it is mainly expressed in cortical areas and limbic system and it has been shown an activity-dependent binding of Npas4 at enhancers (Kim et al., 2010). Ye et al. (2016), reported that there were significant differences between mPFC cells that responded to positive or negative experiences and showed that Npas4 expression was enriched in some mPFC cells in response to cocaine (Ye et al., 2016). Cocaine induced increased Npas4 expression in mPFC occurs within 30 min of cocaine injection (Ye et al., 2016). The authors suggested that Npas4, by controlling distinct networks of genes, may differentially regulate synaptic input to excitatory and inhibitory neurons in order to facilitate circuit responses to various sensory experiences (Spiegel et al., 2014). In this line of evidence, Npas4 was described to be induced by the combination of cocaine and caffeine in the mouse mPFC following conditioned place preference (Muniz et al., 2017).

Finally, it is to be noted that a recent study of gene expression comparing the medial PFC of cocaine addicts to that of control subjects has reported changes in the expression of c-Fos and c-Jun that had previously been identified in animal models of cocaine addiction

**Table 2**
Chronic drug-induced changes on striatal tissues. Abbreviations: morphine withdrawal (MW), self-administration (SA).

| | Cocaine | Methamphetamine | MDMA | Opioids |
|---|---|---|---|---|
| **c-Fos** | ↑[Gao et al., 2017(SA)] | ↓ [Saint-Preux et al., 2013, IP]<br>↑ [Krasnova et al., 2013, SA] | | ↑ [Hayward et al., 1990 (MW); Nye and Nestler, 1996(MW); Georges et al., 2000 (MW)] |
| **FosB** | ↑[Hope et al., 1994; Perrotti et al., 2008; Levine et al., 2005; Larson et al., 2010; Gao et al., 2017(SA) ] | ↓ [Saint-Preux et al., 2013]<br>↑ [Krasnova et al., 2013 (SA)] | | ↑ Nye and Nestler (1996)(MW), Muller and Unterwald (2005) García-Pérez et al. (2012) |
| **Jun family** | | ↓ [Saint-Preux et al., 2013]<br>↑ [Krasnova et al., 2013 (SA)] | | |
| **Fra** | | ↓ [Saint-Preux et al., 2013] | | ↑ [Nye and Nestler, 1996 (MW)] |
| **Egr family** | ↑ [Fritz et al., 2011 (NAc); Muniz et al., 2017 (NAc); Gao et al., 2017(SA)] | ↓ [McCoy et al., 2011; Saint-Preux et al., 2013] | | |
| **Arc** | ↑[Gao et al., 2017(SA)] | | | ↑ [Marie-Claire et al., 2004; Kuntz et al., 2008] |
| **Npas4** | | | | |

(Ribeiro et al., 2017). This study identified activator protein 1 (AP-1) regulated transcriptional network in dlPFC neurons associated with cocaine use disorder that contains several hub genes that are genome-wide association studies (GWAS) hits for traits involved of brain reward (i.e. Body-Mass Index or Obesity) or dlPFC (i.e. Bipolar disorder or Schizophrenia).

*1.2.1.1. Methamphetamine and IEG expression.* Amphetamines are highly addictive synthetic substances that can induce longterm transcriptional and epigenetic changes in the brain (Godino et al., 2015). Amphetamines enter the nerve terminal via the DAT and reverse the direction of the DAT through which large amounts of DA are released (Sulzer et al., 1995). These substances are also substrates for vesicular transporters and can disrupt the concentration of DA with these vesicles by influencing intravesicular pH (Sulzer and Rayport, 1990; Sulzer et al., 2016).

The effects of acute and chronic administration of amphetamine analogs have also been investigated (Cadet et al., 2001; McCoy et al., 2011). Acute administration of amphetamines elicits increased expression of several IEGs whose mRNA levels return rapidly to normal values (Graybiel et al., 1990; Shilling et al., 2006; Cadet et al., 2001). For example, amphetamines cause upregulation of c-Fos expression within1–2 h of their administration in several brain regions of rodents (Graybiel et al., 1990; Shilling et al., 2006; Cadet et al., 2001). In addition to c-Fos expression, Martin et al. (2012) have reported that METH injections can cause significant increases in FosB expression in the NAc. The changes were evident after 1-hr, peaked at 2-hrs, and then reverted back to normal by 24-hr after the drug injection. METH caused smaller mRNA levels increases in c-Jun and JunB mRNA levels that peaked at 1-hr and then returned to normal levels 24 h post-injection (Martin et al., 2012). METH also caused time-dependent decreases in the expression of other genes including Npas4 (Martin et al., 2012). Tomita et al. investigated the effects of a single injection of METH (20 mg/kg) that produced hyperthermia and stereotypic behaviors; they reported increased c-Fos expression in the dorsal striatum, the frontal cortex, anterior hypothalamic area, medial preoptic area, lateral hypothalamic area, paraventricular thalamic nucleus, lateral anterior hypothalamic nucleus, lateral septum, and amygdala. Some of the amphetamine-induced increases in IEG expression are mediated, in part, by activation of striatal DA (D1 and D2) and/or glutamate (NMDA and AMPA) receptors (Gross and Marshall, 2009). Specifically, injections of D1, D2, NMDA, or AMPA receptor antagonists prior to a single systemic injection of METH have been reported to attenuate the effects of methamphetamine on c-Fos expression in the dorsal striatum or cortex (Gross and Marshall, 2009). The early increases in IEG expression are also dependent, in part, on the activation of the CREB signaling pathway via CREB phosphorylation (pCREB) (Torres et al., 2015).

Because amphetamine-induced increases in IEG expression occur very fast and then rapidly return to normal values (Godino et al., 2015), there might be rapid induction of repressive epigenetic regulators that intervene to normalize IEG expression in the rodent brain. This normalization is important to maintain homeostasis in the brain. This suggestion is supported by recently accumulated evidence showing that histone deacetylase 2 (HDAC2) is a negative regular of METH-induced increased expression of some IEGs in the brain. Torres et al. (2015) showed that METH-induced increases in FosB, Fra2, and Egr3 expression were more prolonged in the HDAC2KO mice in comparison to WT mice. In addition, METH caused increased abundance of HDAC2 on the promoters of FosB, Fra2, and Egr3 in WT mice while HDAC2KO mice showed prolonged increased pCREB binding on the promoters of FosB, Fra2, and Egr3. These results suggest that, in the absence of HDAC2, prolonged induction of some IEGs is associated with the activation of the adenylate cyclase/cAMP/PKA/CREB pathway (Torres et al., 2015).

Although acute METH exposure can cause significant increase in the expression of several IEGs, chronic exposure to METH appears to cause opposite effects (McCoy et al., 2011; Saint-Preux et al., 2013). In the NAc, chronic METH decreased the mRNA expression of FosB, fra1, JunB, and fra2 in the NAc but not in the dorsal striatum (Saint-Preux et al., 2013). Chronic METH also decreased NAc egr3 mRNA levels. The Nr4a family member, nr4a2/nurr1, showed increased striatal expression following chronic METH injections (Saint-Preux et al., 2013). These results support the accumulated evidence that chronic administration of psychostimulants is associated with blunting of their acute stimulatory effects on IEG expression. Interestingly, it was also reported that an acute METH challenge was able to normalize the expression of c-Fos, Erg1-3, and Nr4a1 in the striatum of rats chronically treated with METH (McCoy et al., 2011). Because these IEGs regulate the expression of many genes, it is possible that these chronic drug effects might trigger critical transcriptional responses that drive compensatory neuroadaptations. Moreover, there is some indication that chronic METH might produce region-dependent effects within the striatum to Fos reactivity (Jedynak et al., 2012). A METH challenge increased the number of c-Fos positive cells in all areas of the dorsal and ventral striatum, but these effects were observed in more cells in the patch than in the matrix compartment in the dorsolateral and dorsomedial caudate-putamen (Jedynak et al., 2012).

Using the extended-access METH self-administration procedure, Cadet's group found that the expression of c-Fos, c-Jun, Crem, FosB, Nptx1, Nptx2, and Nr4a1-3 was increased at 2 h after cessation of METH self-administration (Krasnova et al., 2013). These changes were no longer present at one month after withdrawal, except for decreases in JunD and ΔFosB levels (Krasnova et al., 2013). Because JunD and ΔFosB are binding partners and because deltaFosB is also a key regulator in gene expression in other models of drug addiction, our findings suggest that, together, the downregulation of both JunD and ΔFosB model might serve to generate the increased motoric behaviors (e.g., increased lever presses) observed after lengthy withdrawal from methamphetamine self-administration (Cadet et al., 2015).

*1.2.1.2. Methamphetamine, IEGs, and neurodegeneration.* As mentioned above, amphetamine analogs can cause massive DA release in the cytoplasm followed by increases in DA concentration in the synaptic cleft in brain regions that receive dopaminergic projections from the midbrain. Autoxidation and metabolism of synaptic DA can generate reactive oxygen species (ROS) (Cadet, 1988; Cadet and Brannock, 1998) that might be partial causes of METH toxicity (Cadet et al., 1994)as represented by DA depletion (Raineri et al., 2011). Astroglial and microglial activation (Raineri et al., 2012, 2015) as well as decreased DAT protein expression (German et al., 2012) in the striatum are also manifestations of amphetamine toxicity. Humans exposed to METH also show pathological changes in their brains (Cadet et al., 2014).

IEGs appear to also be involved in METH toxicity. For example, Hirata et al. (1998) had reported that superoxide radicals played an important role in the activation of Zif268 (Egr1) after METH administration. The presence of c-Fos appears to play a protective role against METH-induced damage because METH toxicity is exacerbated in c-fos heterozygous knockout mice, suggesting that METH can induced pathological cascades that trigger a general toxic response after injections of toxic doses of the drug (Cadet et al., 2002). A single, toxic, injection of METH (40 mg/kg) increased Egr-1 and c-Fos mRNA levels within 30 min in the rodent frontal cortex, nucleus accumbens, caudate putamen, septum, and CA1 region of hippocampus. mRNA levels of both genes were increased within 30 min and returned to baseline after 60 min (Thiriet et al., 2001).

METH toxicity was also evaluated using FosB null mutant (−/−) mice (Kuroda et al., 2010). This study showed that three days after administration of four 10 mg/kg METH injections, the frontoparietal cortex and striatum of FosB(−/−) mice contained more degenerated neurons (by Fluoro-Jade B staining) and markers of blood-brain barrier dysfunction. Together, these observations indicate that both c-Fos and FosB might play protective role against METH toxicity.

Some of the increases in IEG mRNA levels after toxic doses of METH appear to be dependent on DA D1 receptor activation (Beauvais et al., 2010). Binge injections of METH (10 mg/kg x 4 every 2 h) caused significant increases in c-Fos and fra2 expression lasting from 30 min to 4 h (Beauvais et al., 2010). Pre-treatment with a DA D1 antagonist, SCh23390, completely blocked METH-induced expression of c-Fos while partially inhibiting fra-2 mRNA expression. The D1 antagonist-mediated suppression of basal fra-1, egr-1, and egr-2 mRNA levels also suggests that their basal expression in the striatum might be dependent on tonic stimulation of the DA D1 receptor (Beauvais et al., 2010). METH-induced neuroplasticity triggered by toxicity is thought to have profound residual effects. Belcher et al. (2009) investigated cortical and subcortical IEG expression in rats long after (five weeks) administration of a single-day METH toxic regimen (4 × 4 mg/kg, s.c.). Compared with saline-pretreated controls, METH-pretreated animals had about 50–70% fewer c-Fos- and JunB-immunoreactive cells in the striatum, anterior cingulate, infralimbic, orbital, somatosensory, and rhinal cortices 90 min after an apomorphine challenge. These results are also consistent with other reports that demonstrated an attenuation of the acute METH-induced effects on Egr2 expression in METH-pretreated rats (Cadet et al., 2013).

#### 1.2.2. 3,4-Methylenedioxymethamphetamine and IEG expression

3,4-Methylenedioxymethamphetamine (MDMA or "Ecstasy") is a recreational drug that exhibits both stimulatory and hallucinogenic properties. Ecstasy differs from amphetamine and methamphetamine in that it has a methylenedioxy (—O—CH2-O—) group attached to the aromatic ring of the amphetamine molecule. Thus, its chemical structure resembles the structure of the hallucinogenic material mescaline. MDMA is a popular "rave drug" that can enhance social intimacy, increase feelings of euphoria and energy (Green et al., 1995). MDMA binds and blocks all monoamine transporters but exhibit a higher affinity for the serotonin transporter (SERT) thus the net neurochemical effect is increased serotonin release and availability into the synapse (Green et al., 1995).

Similarly to other amphetamine derivatives, MDMA is capable of inducing rapid and transient expression of several IEGs in the CNS. Acute MDMA administration cause marked expression of c-Fos (protein) in several regions of rat brain. The NAc, striatum, septum and some nuclei of the hypothalamus responded to MDMA (Erdtmann-Vourliotis et al., 1999). Acute MDMA also alters the expression of egr-1 mRNA in several regions of rat brain, (the prefrontal cortex, striatum and dentate gyrus of the hippocampus), changes that appear to be mediated, at least in part, by NMDA receptor, DA D1 receptor, and 5-HT transporter (Shirayama et al., 2000).

The ERK-dependent pathway is differentially implicated in IEG transcription depending on the brain regions and the IEG under study (Salzmann et al., 2003; Benturquia et al., 2008). For example, an acute intraperitoneal injection of MDMA induces strong c-Fos transcription in the dorsal striatum, NAc, and hippocampus but Egr1 and Egr3 transcripts were increased only in the striatum (Salzmann et al., 2003). MDMA-induced changes in IEG mRNA expression were selectively suppressed by an ERK inhibitor in the caudate putamen, suggesting a role for other signaling pathways in regulating IEG transcription in other brain structures. These findings are consistent with those of Benturquia et al. (2008), who also reported that the ERK pathway is involved in MDMA-mediated induction of c-Fos, FosB, Egr1 and Egr2 in the striatum.

High ambient temperature increases MDMA-induced hyperthermia and potential neurotoxic consequences (Cadet et al., 2014). MDMA-induced c-Fos expression was increased in several brain regions at the high temperature. These regions include hypothalamic areas that are linked to thermoregulation (median preoptic nucleus, dorsomedial hypothalamus) and oxytocin and vasopressin expression (supraoptic nucleus), as well as the medial and central nuclei of the amygdala. They also include the NAc and VTA, two brain regions that are associated with the reinforcing effects of MDMA (Hargreaves et al., 2007). It is also of interest to mention another study that had reported found that a neurotoxic dose of MDMA that induced hyperthermia can induce Arc expression in the cortex and CA1 area of the hippocampus, changes that, importantly, occurred independent of 5-HT depletion (Beveridge et al., 2004).

### 1.3. Regulation of IEGs by opioid drugs

MOR-selective agonists such as morphine, fentanyl, and oxycodone are the most effective analgesics currently available, but their clinical utility is limited due to their induction of tolerance and dependence, propensity for misuse, and risk of overdose ( ; Kreek et al. (2012). The main active metabolites of heroin and abused prescription opioids act primarily as agonists at Mu Opioid Receptor (MOP-r). Once in the brain, heroin is rapidly converted to the biologically active metabolites morphine and monoacetylmorphine (Kreek et al., 2012).

AP-1 DNA binding factors are regulated by morphine. A single injection of morphine (10 mg/kg) was reported to induce the expression of c-Fos and JunB in the rat striatum and NAc by mechanisms that include stimulation of DA D1 and NMDA receptors (Liu et al., 1994), (see Table 1). In addition, acute morphine induced ΔFosB was dependent on DA D1 receptors activation (Muller and Unterwald, 2005).

The stimulatory effect of systemic morphine on striatal and accumbal c-Fos, which is DA-mediated, appear to be indirect resulting from predominant disinhibition of mesolimbic and nigrostriatal dopaminergic neurons by the suppression of GABA-interneurons in the VTA and SN. (Bontempi and Sharp, 1997; Steffensen et al., 2006). However, there is evidence of opioid-induced activation of IEGs (c-Fos and JunB) in MOP-r-expressing cells in cultures (Shoda et al., 2001).

Opiates are known triggers for Egr1 expression in several brain areas. In particular, an acute heroin injection up-regulates Egr1 mRNA levels in the core and shell of the NAc, the dorsal striatum, and the mouse cingulate cortex (El Rawas et al., 2009). Similarly, increased Egr1 expression levels are observed in the extended amygdala, dorsal striatum, NAc, and cingulate cortex following an acute morphine injection (Hamlin et al., 2007; Ziółkowska et al., 2012, 2015). Notably, the latter is observed 4 h and 6 h following injection, which suggests that in this context, Egr1 up-regulation is part of a second wave of gene regulations Ziółkowska et al. (2015). This profile of delayed up-regulation of several IEG in the striatum after morphine administration was also reported for c-Fos and Arc (Piechota et al., 2010; Ziółkowska et al., 2012). This somehow differential feature (in comparison with acute psychostimulant –induced response on IEGs) may contribute to the development of long-term effects of opioids such as tolerance or dependence (Ziółkowska et al., 2015).

It is of interest that chronic morphine administration can also induce FosB/ΔFosB in several brain areas that include the NAc, bed nucleus of the stria terminalis (BNST), central amygdala (CeA), hypothalamic paraventricular nucleus (PVN) and nucleus of the solitary tract (García-Pérez et al., 2012). It is to be noted that these changes can be attenuated by adrenalectomy, suggesting that they might be partially dependent on peripheral mechanisms triggered by adrenal hormones (García-Pérez et al., 2012). Also of interest is the observation that rewarding properties of morphine were abolished in FosB knockout mice (Solecki et al., 2008), thus suggesting very important links between reward and IEG responses induced by opioid drugs.

Arc (activity-regulated cytoskeleton-associated protein) is classified as an immediate-early gene because of its rapid induction after stimulation. Chronic morphine produced a significant increase in the mRNA and protein levels of Arc in rat striatum (Marie-Claire et al., 2004), see Table 2. The exact function of Arc is unknown but its induction and localization in dendrites and soma (Steward and Worley, 2001) suggested its involvement in the process of synaptic plasticity (Lyford et al., 1995). Since Arc mRNA has a short half-life (Steward and Worley, 2001), therefore Arc upregulation is unlikely to result from a direct

action of morphine, but rather from long-term adaptations at dendrites. This supports the modification of dendritic branching observed following chronic morphine treatment (Robinson and Kolb, 1999).

IEG expression in the PFC in particular was increased in activated neurons while expression was unaltered in non-activated neurons. Cue-induced heroin seeking was associated with increased mRNA expression of Arc, FosB, Egr1, and Egr2 in only c-Fos-positive PFC neurons but not in c-Fos-negative neurons obtained from the same tissue (Fanous et al., 2013).

### 1.4. IEG expression induced by opioid withdrawal

Opiate withdrawal is characterized by both somatic and motivational behavioral signs upon cessation of drug use, and represents a classical feature of opiate dependence (for review: Koob et al., 1992). The experience of withdrawal promotes the emergence of a negative affective state. Naltrexone in opioid dependent individuals will result in an acute block of opioid receptors and precipitate a severe opioid withdrawal reaction. Early morphine withdrawal studies demonstrated robust induction of several known acute Fras, including c-Fos, FosB, Fra-1, Fra-2, and delta FosB, at 6 h after naltrexone precipitation of withdrawal in the striatum, NAc, and several other brain regions. (Nye and Nestler, 1996). One hour after injection of naltrexone to morphine-dependent rats, c-Fos mRNA was induced in the projecting areas of the dopaminergic neurons (NAc, CPu, prefrontal cortex, olfactory tubercle), of noradrenergic neurons (BNST, amygdala nuclei, septal areas), and in several other brain regions expressing opiate receptors (locus coeruleus, thalamus, hypothalamus, cortex) (Georges et al., 2000). Morphine withdrawal induced a differential c-Fos expression in the two efferent populations of the striatum (striatonigral versus striatopallidal) (Georges et al., 2000).

Egr1 is also involved in neuroadaptations underlying long-lasting effects of morphine exposure, such as withdrawal and relapse. Consequently, naloxone-induced morphine withdrawal in rats induces an Egr1 up-regulation in the cerebral cortex, hippocampus, thalamus, cerebellum, and brainstem 60 min following the withdrawal (Beckmann et al., 1995). Similarly, Egr1 and its target, Arc, are up-regulated in the rat dentate gyrus upon morphine-withdrawal memory retrieval, suggesting that Egr1 could be involved in the synaptic plasticity events underlying reconsolidation of the morphine withdrawal-context (García-Pérez et al., 2016).

Re-exposure to drug-related cues elicits drug-seeking behavior and relapse in both humans and laboratory animals even after months of abstinence. Several studies were aimed to identify neural and molecular substrates underlying conditioned heroin-seeking behavior linked to relapse behaviors. Accordingly, IEG expression patterns were measured in mesocorticolimbic system target areas following cue-induced reinstatement of heroin seeking (Koya et al., 2006). Exposure to the cue after 3 weeks of withdrawal reinstated heroin-seeking behavior and resulted in increased expression of ania-3, MKP-1, c-Fos and Nr4a3 in the medial prefrontal cortex (mPFC) (Koya et al., 2006). Consistent with a significant interplay between the amygdala and the mPFC during cue-associated memory reactivation, extinction, and/or reconsolidation, increased Egr1 mRNA levels were also found in the rat mPFC following 14 or 30 days of heroin-seeking incubation (Kuntz et al., 2008; Kuntz-Melcavage et al., 2009; Fanous et al., 2013).

## 2. Concluding remarks

Psychostimulants and opioid drugs are addictive drugs that act, respectively, on monoamine transporters and opioid receptors located in brain regions that subsume reward, decision making, and memory formation. The chronic use of these drugs is associated with divergent clinical consequences in patients who suffer from addiction to these various classes of these drugs. As described above, the acute and longterm molecular and cellular effects of these drugs include activation of various genes that can act as transcription factors in the brain. The acute and long-term effects on IEG expression might trigger downstream events that may be relevant to the clinical course of the beneficial and adverse effects of these classes of thee abusable substances. This interpretation suggests that better understanding of the pathways that are activated by these IEG cascades may lead to better therapeutic approaches against addiction to psychostimulants or opioid agents. Future studies that involve manipulation of the levels of these IEGs in the context of drug self-administration should identify their specific role in substance use disorders.

## Acknowledgments

The Intramural Research Program of the National Institute on Drug Abuse, NIH, and DHHS supports Jean Lud Cadet. Veronica Bisagno is supported by a grant from ANPCyT, PICT 2015–2594, Argentina.

## References

Amara, S.G., Sonders, M.S., 1998 Jun-Jul. Neurotransmitter transporters as molecular targets for addictive drugs. Drug Alcohol Depend. 51 (1–2), 87–96.
Badiani, A., Belin, D., Epstein, D., Calu, D., Shaham, Y., 2011 Oct 5. Opiate versus psychostimulant addiction: the differences do matter. Nat. Rev. Neurosci. 12 (11), 685–700. https://doi.org/10.1038/nrn3104.
Bahrami, S., Drabløs, F., 2016 Sep. Gene regulation in the immediate-early response process. Adv Biol Regul 62, 37–49. https://doi.org/10.1016/j.jbior.2016.05.001.
Beauvais, G., Jayanthi, S., McCoy, M.T., Ladenheim, B., Cadet, J.L., 2010 Mar 8. Differential effects of methamphetamine and SCH23390 on the expression of members of IEG families of transcription factors in the rat striatum. Brain Res. 1318, 1–10. https://doi.org/10.1016/j.brainres.2009.12.083.
Beckmann, A.M., Matsumoto, I., Wilce, P.A., 1995 Sep. Immediate early gene expression during morphine withdrawal. Neuropharmacology 34 (9), 1183–1189.
Belcher, A.M., O'Dell, S.J., Marshall, J.F., 2009 May. Long-term changes in dopamine-stimulated gene expression after single-day methamphetamine exposure. Synapse 63 (5), 403–412. https://doi.org/10.1002/syn.20617.
Benturquia, N., Courtin, C., Noble, F., Marie-Claire, C., 2008 May 23. Involvement of D1 dopamine receptor in MDMA-induced locomotor activity and striatal gene expression in mice. Brain Res. 1211, 1–5. https://doi.org/10.1016/j.brainres.2008.03.016.
Beveridge, T.J., Mechan, A.O., Sprakes, M., Pei, Q., Zetterstrom, T.S., Green, A.R., Elliott, J.M., 2004 May. Effect of 5-HT depletion by MDMA on hyperthermia and Arc mRNA induction in rat brain. Psychopharmacology (Berlin) 173 (3–4), 346–352.
Blackwood, C.A., Hoerle, R., Leary, M., Schroeder, J., Job, M.O., McCoy, M.T., Ladenheim, B., Jayanthi, S., Cadet, J.L., 2018 Aug 28. Molecular adaptations in the rat dorsal striatum and Hippocampus following abstinence-induced incubation of drug seeking after escalated oxycodone self-administration. Mol. Neurobiol. https://doi.org/10.1007/s12035-018-1318-z.
Bontempi, B., Sharp, F.R., 1997 Nov 1. Systemic morphine-induced Fos protein in the rat striatum and nucleus accumbens is regulated by mu opioid receptors in the substantia nigra and ventral tegmental area. J. Neurosci. 17 (21), 8596–8612.
Cadet, J.L., 1988 May. Free radical mechanisms in the central nervous system: an overview. Int. J. Neurosci. 40 (1–2), 13–18.
Cadet, J.L., 1994 May. Free radicals and neurodegeneration. Trends Neurosci. 17 (5), 192–194.
Cadet, J.L., 2016 Jan. Epigenetics of stress, addiction, and resilience: therapeutic implications. Mol. Neurobiol. 53 (1), 545–560. https://doi.org/10.1007/s12035-014-9040-y.
Cadet, J.L., Bisagno, V., 2013 Nov 18. The primacy of cognition in the manifestations of substance use disorders. Front. Neurol. 4, 189. https://doi.org/10.3389/fneur.2013.00189.
Cadet, J.L., Bisagno, V., Milroy, C.M., 2014 Jan. Neuropathology of substance use disorders. Acta Neuropathol. 127 (1), 91–107. https://doi.org/10.1007/s00401-013-1221-7.
Cadet, J.L., Brannock, C., 1998 Feb. Free radicals and the pathobiology of brain dopamine systems. Neurochem. Int. 32 (2), 117–131.
Cadet, J.L., Krasnova, I.N., Walther, D., Brannock, C., Ladenheim, B., McCoy, M.T., Collector, D., Torres, O.V., Terry, N., Jayanthi, S., 2016 Nov 14. Increased expression of proenkephalin and prodynorphin mRNAs in the nucleus accumbens of compulsive methamphetamine taking rats. Sci. Rep. 6, 37002. https://doi.org/10.1038/srep37002.
Cadet, J.L., Brannock, C., Jayanthi, S., Krasnova, I.N., 2015 Apr. Transcriptional and epigenetic substrates of methamphetamine addiction and withdrawal: evidence from a long-access self-administration model in the rat. Mol. Neurobiol. 51 (2), 696–717. https://doi.org/10.1007/s12035-014-8776-8.
Cadet, J.L., Jayanthi, S., McCoy, M.T., Vawter, M., Ladenheim, B., 2001 Jul. Temporal profiling of methamphetamine-induced changes in gene expression in the mouse brain: evidence from cDNA array. Synapse 41 (1), 40–48.
Cadet, J.L., McCoy, M.T., Ladenheim, B., 2002 Jun 15. Distinct gene expression signatures in the striata of wild-type and heterozygous c-fos knockout mice following methamphetamine administration: evidence from cDNA array analyses. Synapse 44 (4), 211–226.

Cadet, J.L., Jayanthi, S., McCoy, M.T., Ladenheim, B., Saint-Preux, F., Lehrmann, E., De, S., Becker, K.G., Brannock, C., 2013 Aug 12. Genome-wide profiling identifies a subset of methamphetamine (METH)-induced genes associated with METH-induced increased H4K5Ac binding in the rat striatum. BMC Genomics 14, 545. https://doi.org/10.1186/1471-2164-14-545.

Chen, J., Nye, H.E., Kelz, M.B., Hiroi, N., Nakabeppu, Y., Hope, B.T., Nestler, E.J., 1995 Nov. Regulation of delta FosB and FosB-like proteins by electroconvulsive seizure and cocaine treatments. Mol. Pharmacol. 48 (5), 880–889.

Chen, J., Kelz, M.B., Hope, B.T., Nakabeppu, Y., Nestler, E.J., 1997 Jul 1. Chronic Fos-related antigens: stable variants of deltaFosB induced in brain by chronic treatments. J. Neurosci. 17 (13), 4933–4941.

Chesselet, M.F., Chéramy, A., Reisine, T.D., Glowinski, J., 1981 May 28. Morphine and delta-opiate agonists locally stimulate in vivo dopamine release in cat caudate nucleus. Nature 291 (5813), 320–322.

Cruz, F.C., Quadros, I.M., Hogenelst, K., Planeta, C.S., Miczek, K.A., 2011. Social defeat stress in rats: escalation of cocaine and “speedball” binge self-administration, but not heroin. Psychopharmacology 215, 165–175.

Dalley, J.W., Fryer, T.D., Brichard, L., Robinson, E.S., Theobald, D.E., Lääne, K., Peña, Y., Murphy, E.R., Shah, Y., Probst, K., Abakumova, I., Aigbirhio, F.I., Richards, H.K., Hong, Y., Baron, J.C., Everitt, B.J., Robbins, T.W., 2007 Mar 2. Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. Science 315 (5816), 1267–1270.

El Rawas, R., Thiriet, N., Lardeux, V., Jaber, M., Solinas, M., 2009 Apr. Environmental enrichment decreases the rewarding but not the activating effects of heroin. Psychopharmacology (Berlin) 203 (3), 561–570. https://doi.org/10.1007/s00213-008-1402-6.

Erdtmann-Vourliotis, M., Mayer, P., Riechert, U., Höllt, V., 1999 Aug 25. Acute injection of drugs with low addictive potential (delta(9)-tetrahydrocannabinol, 3,4-methylenedioxymethamphetamine, lysergic acid diamide) causes a much higher c-fos expression in limbic brain areas than highly addicting drugs (cocaine and morphine). Brain Res Mol Brain Res 71 (2), 313–324.

Fanous, S., Guez-Barber, D.H., Goldart, E.M., Schrama, R., Theberge, F.R., Shaham, Y., Hope, B.T., 2013 Jan. Unique gene alterations are induced in FACS-purified Fos-positive neurons activated during cue-induced relapse to heroin seeking. J. Neurochem. 124 (1), 100–108. https://doi.org/10.1111/jnc.12074.

Fritz, M., El Rawas, R., Salti, A., Klement, S., Bardo, M.T., Kemmler, G., Dechant, G., Saria, A., Zernig, G., 2011 Apr. Reversal of cocaine-conditioned place preference and mesocorticolimbic Zif268 expression by social interaction in rats. Addict. Biol. 16 (2), 273–284. https://doi.org/10.1111/j.1369-1600.2010.00285.x.

Graybiel, A.M., Moratalla, R., Robertson, H.A., 1990 Sep. Amphetamine and cocaine induce drug-specific activation of the c-fos gene in striosome-matrix compartments and limbic subdivisions of the striatum. Proc. Natl. Acad. Sci. U. S. A. 87 (17), 6912–6916.

García-Pérez, D., Ferenczi, S., Kovács, K.J., Laorden, M.L., Milanés, M.V., Núñez, C., 2016 Dec. Different contribution of glucocorticoids in the basolateral amygdala to the formation and expression of opiate withdrawal-associated memories. Psychoneuroendocrinology 74, 350–362. https://doi.org/10.1016/j.psyneuen.2016.09.020.

García-Pérez, D., Laorden, M.L., Milanés, M.V., Núñez, C., 2012. Glucocorticoids regulation of FosB/ΔFosB expression induced by chronic opiate exposure in the brain stress system. PLoS One 7 (11), e50264. https://doi.org/10.1371/journal.pone.0050264.

Gao, P., Limpens, J.H., Spijker, S., Vanderschuren, L.J., Voorn, P., 2017 Mar. Stable immediate early gene expression patterns in medial prefrontal cortex and striatum after long-term cocaine self-administration. Addict. Biol. 22 (2), 354–368. https://doi.org/10.1111/adb.12330.

German, C.L., Hanson, G.R., Fleckenstein, A.E., 2012 Oct. Amphetamine and methamphetamine reduce striatal dopamine transporter function without concurrent dopamine transporter relocalization. J. Neurochem. 123 (2), 288–297. https://doi.org/10.1111/j.1471-4159.2012.07875.x.

Georges, F., Stinus, L., Le Moine, C., 2000 Dec. Mapping of c-fos gene expression in the brain during morphine dependence and precipitated withdrawal, and phenotypic identification of the striatal neurons involved. Eur. J. Neurosci. 12 (12), 4475–4486.

Godino, A., Jayanthi, S., Cadet, J.L., 2015. Epigenetic landscape of amphetamine and methamphetamine addiction in rodents. Epigenetics 10 (7), 574–580. https://doi.org/10.1080/15592294.2015.1055441.

Goldstein, R.Z., Volkow, N.D., 2011 Oct 20. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nat. Rev. Neurosci. 12 (11), 652–669. https://doi.org/10.1038/nrn3119.

Green, A.R., Cross, A.J., Goodwin, G.M., 1995 Jun. Review of the pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA or "Ecstasy"). Psychopharmacology (Berlin) 119 (3), 247–260.

Gross, N.B., Marshall, J.F., 2009 Jul 21. Striatal dopamine and glutamate receptors modulate methamphetamine-induced cortical Fos expression. Neuroscience 161 (4), 1114–1125. https://doi.org/10.1016/j.neuroscience.2009.04.023.

Guez-Barber, D., Fanous, S., Golden, S.A., Schrama, R., Koya, E., Stern, A.L., Bossert, J.M., Harvey, B.K., Picciotto, M.R., Hope, B.T., 2011 Mar 16. FACS identifies unique cocaine-induced gene regulation in selectively activated adult striatal neurons. J. Neurosci. 31 (11), 4251–4259. https://doi.org/10.1523/JNEUROSCI.6195-10.2011.

Hamlin, A.S., McNally, G.P., Osborne, P.B., 2007 Aug. Induction of c-Fos and zif268 in the nociceptive amygdala parallel abstinence hyperalgesia in rats briefly exposed to morphine. Neuropharmacology 53 (2), 330–343.

Hargreaves, G.A., Hunt, G.E., Cornish, J.L., McGregor, I.S., 2007 Mar 16. High ambient temperature increases 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy")-induced Fos expression in a region-specific manner. Neuroscience 145 (2), 764–774.

Hedegaard, H., Warner, M., Miniño, A.M., 2017 Dec. Drug overdose deaths in the United States, 1999-2016. NCHS Data Brief (294), 1–8 PubMed PMID: 29319475.

Hirata, H., Asanuma, M., Cadet, J.L., 1998 Jul 15. Superoxide radicals are mediators of the effects of methamphetamine on Zif268 (Egr-1, NGFI-A) in the brain: evidence from using CuZn superoxide dismutase transgenic mice. Brain Res Mol Brain Res 58 (1–2), 209–216.

Hope, B., Kosofsky, B., Hyman, S.E., Nestler, E.J., 1992 Jul 1. Regulation of immediate early gene expression and AP-1 binding in the rat nucleus accumbens by chronic cocaine. Proc. Natl. Acad. Sci. U. S. A. 89 (13), 5764–5768.

Hope, B.T., Nye, H.E., Kelz, M.B., Self, D.W., Iadarola, M.J., Nakabeppu, Y., Duman, R.S., Nestler, E.J., 1994 Nov. Induction of a long-lasting AP-1 complex composed of altered Fos-like proteins in brain by chronic cocaine and other chronic treatments. Neuron 13 (5), 1235–1244.

Hayward, M.D., Duman, R.S., Nestler, E.J., 1990 Aug 20. Induction of the c-fos proto-oncogene during opiate withdrawal in the locus coeruleus and other regions of rat brain. Brain Res. 525 (2), 256–266.

Jedynak, J.P., Cameron, C.M., Robinson, T.E., 2012. Repeated methamphetamine administration differentially alters fos expression in caudate-putamen patch and matrix compartments and nucleus accumbens. PLoS One 7 (4), e34227. https://doi.org/10.1371/journal.pone.0034227.

Kim, T.K., Hemberg, M., Gray, J.M., Costa, A.M., Bear, D.M., Wu, J., Harmin, D.A., Laptewicz, M., Barbara-Haley, K., Kuersten, S., Markenscoff-Papadimitriou, E., Kuhl, D., Bito, H., Worley, P.F., Kreiman, G., Greenberg, M.E., 2010 May 13. Widespread transcription at neuronal activity-regulated enhancers. Nature 465 (7295), 182–187. https://doi.org/10.1038/nature09033.

Koya, E., Spijker, S., Voorn, P., Binnekade, R., Schmidt, E.D., Schoffelmeer, A.N., De Vries, T.J., Smit, A.B., 2006 Aug. Enhanced cortical and accumbal molecular reactivity associated with conditioned heroin, but not sucrose-seeking behaviour. J. Neurochem. 98 (3), 905–915.

Krasnova, I.N., Chiflikyan, M., Justinova, Z., McCoy, M.T., Ladenheim, B., Jayanthi, S., Quintero, C., Brannock, C., Barnes, C., Adair, J.E., Lehrmann, E., Kobeissy, F.H., Gold, M.S., Becker, K.G., Goldberg, S.R., Cadet, J.L., 2013 Oct. CREB phosphorylation regulates striatal transcriptional responses in the self-administration model of methamphetamine addiction in the rat. Neurobiol. Dis. 58, 132–143. https://doi.org/10.1016/j.nbd.2013.05.009.

Kreek, M.J., Levran, O., Reed, B., Schlussman, S.D., Zhou, Y., Butelman, E.R., 2012 Oct. Opiate addiction and cocaine addiction: underlying molecular neurobiology and genetics. J. Clin. Invest. 122 (10), 3387–3393. https://doi.org/10.1172/JCI60390.

Kristensen, A.S., Andersen, J., Jørgensen, T.N., Sørensen, L., Eriksen, J., Loland, C.J., Strømgaard, K., Gether, U., 2011 Sep. SLC6 neurotransmitter transporters: structure, function, and regulation. Pharmacol. Rev. 63 (3), 585–640. https://doi.org/10.1124/pr.108.000869.

Koob, G.F., 1992 May. Drugs of abuse: anatomy, pharmacology and function of reward pathways. Trends Pharmacol. Sci. 13 (5), 177–184.

Koob, G.F., Volkow, N.D., 2010 Jan. Neurocircuitry of addiction. Neuropsychopharmacology 35 (1), 217–238. https://doi.org/10.1038/npp.2009.110. Review. Erratum in: Neuropsychopharmacology. 2010 Mar;35(4):1051.

Koob, G.F., Volkow, N.D., 2016 Aug. Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry 3 (8), 760–773. https://doi.org/10.1016/S2215-0366(16)00104-8.

Kufahl, P.R., Zavala, A.R., Singh, A., Thiel, K.J., Dickey, E.D., Joyce, J.N., Neisewander, J.L., 2009 Oct. c-Fos expression associated with reinstatement of cocaine-seeking behavior by response-contingent conditioned cues. Synapse 63 (10), 823–835. https://doi.org/10.1002/syn.20666.

Kuhar, M.J., Ritz, M.C., Boja, J.W., 1991 Jul. The dopamine hypothesis of the reinforcing properties of cocaine. Trends Neurosci. 14 (7), 299–302.

Kuntz, K.L., Patel, K.M., Grigson, P.S., Freeman, W.M., Vrana, K.E., 2008 Sep. Heroin self-administration: II. CNS gene expression following withdrawal and cue-induced drug-seeking behavior. Pharmacol. Biochem. Behav. 90 (3), 349–356. https://doi.org/10.1016/j.pbb.2008.03.019.

Kuntz-Melcavage, K.L., Brucklacher, R.M., Grigson, P.S., Freeman, W.M., Vrana, K.E., 2009 Aug 7. Gene expression changes following extinction testing in a heroin behavioral incubation model. BMC Neurosci. 10, 95. https://doi.org/10.1186/1471-2202-10-95.

Kuroda, K.O., Ornthanalai, V.G., Kato, T., Murphy, N.P., 2010 Feb. FosB null mutant mice show enhanced methamphetamine neurotoxicity: potential involvement of FosB in intracellular feedback signaling and astroglial function. Neuropsychopharmacology 35 (3), 641–655. https://doi.org/10.1038/npp.2009.169.

Larson, E.B., Akkentli, F., Edwards, S., Graham, D.L., Simmons, D.L., Alibhai, I.N., Nestler, E.J., Self, D.W., 2010 Oct. Striatal regulation of ΔFosB, FosB, and cFos during cocaine self-administration and withdrawal. J. Neurochem. 115 (1), 112–122. https://doi.org/10.1111/j.1471-4159.2010.06907.x.

Leone, P., Pocock, D., Wise, R.A., 1991 Jun. Morphine-dopamine interaction: ventral tegmental morphine increases nucleus accumbens dopamine release. Pharmacol. Biochem. Behav. 39 (2), 469–472.

Leslie, J.H., Nedivi, E., 2011 Aug. Activity-regulated genes as mediators of neural circuit plasticity. Prog. Neurobiol. 94 (3), 223–237. https://doi.org/10.1016/j.pneurobio.2011.05.002.

Levine, A.A., Guan, Z., Barco, A., Xu, S., Kandel, E.R., Schwartz, J.H., 2005 Dec 27. CREB-binding protein controls response to cocaine by acetylating histones at the fosB promoter in the mouse striatum. Proc. Natl. Acad. Sci. U. S. A. 102 (52), 19186–19191.

Liu, J., Nickolenko, J., Sharp, F.R., 1994 Aug 30. Morphine induces c-fos and junB in striatum and nucleus accumbens via D1 and N-methyl-D-aspartate receptors. Proc. Natl. Acad. Sci. U. S. A. 91 (18), 8537–8541.

Liu, Q.R., Rubio, F.J., Bossert, J.M., Marchant, N.J., Fanous, S., Hou, X., Shaham, Y., Hope, B.T., 2014 Jan. Detection of molecular alterations in methamphetamine-activated Fos-expressing neurons from a single rat dorsal striatum using fluorescence-

activated cell sorting (FACS). J. Neurochem. 128 (1), 173–185. https://doi.org/10.1111/jnc.12381.
Lyford, G.L., Yamagata, K., Kaufmann, W.E., Barnes, C.A., Sanders, L.K., Copeland, N.G., Gilbert, D.J., Jenkins, N.A., Lanahan, A.A., Worley, P.F., 1995 Feb. Arc, a growth factor and activity-regulated gene, encodes a novel cytoskeleton-associated protein that is enriched in neuronal dendrites. Neuron 14 (2), 433–445.
Marie-Claire, C., Courtin, C., Roques, B.P., Noble, F., 2004 Dec. Cytoskeletal genes regulation by chronic morphine treatment in rat striatum. Neuropsychopharmacology 29 (12), 2208–2215.
Martin, T.A., Jayanthi, S., McCoy, M.T., Brannock, C., Ladenheim, B., Garrett, T., Lehrmann, E., Becker, K.G., Cadet, J.L., 2012. Methamphetamine causes differential alterations in gene expression and patterns of histone acetylation/hypoacetylation in the rat nucleus accumbens. PLoS One 7 (3), e34236. https://doi.org/10.1371/journal.pone.0034236.
McCoy, M.T., Jayanthi, S., Wulu, J.A., Beauvais, G., Ladenheim, B., Martin, T.A., Krasnova, I.N., Hodges, A.B., Cadet, J.L., 2011 May. Chronic methamphetamine exposure suppresses the striatal expression of members of multiple families of immediate early genes (IEGs) in the rat: normalization by an acute methamphetamine injection. Psychopharmacology (Berlin) 215 (2), 353–365. https://doi.org/10.1007/s00213-010-2146-7.
McNamara, R., Dalley, J.W., Robbins, T.W., Everitt, B.J., Belin, D., 2010. Trait-like impulsivity does not predict escalation of heroin self-administration in the rat. Psychopharmacology 212, 453–464.
Muller, D.L., Unterwald, E.M., 2005 Jul. D1 dopamine receptors modulate deltaFosB induction in rat striatum after intermittent morphine administration. J. Pharmacol. Exp. Therapeut. 314 (1), 148–154.
Muñiz, J.A., Prieto, J.P., González, B., Sosa, M.H., Cadet, J.L., Scorza, C., Urbano, F.J., Bisagno, V., 2017 Oct 18. Cocaine and caffeine effects on the conditioned place preference test: concomitant changes on early genes within the mouse prefrontal cortex and nucleus accumbens. Front. Behav. Neurosci. 11, 200. https://doi.org/10.3389/fnbeh.2017.00200.
Nestler, E.J., Barrot, M., Self, D.W., 2001 Sep 25. DeltaFosB: a sustained molecular switch for addiction. Proc. Natl. Acad. Sci. U. S. A. 98 (20), 11042–11046.
Nelson, R.A., Boyd, S.J., Ziegelstein, R.C., Herning, R., Cadet, J.L., Henningfield, J.E., Schuster, C.R., Contoreggi, C., Gorelick, D.A., 2006 Mar 15. Effect of rate of administration on subjective and physiological effects of intravenous cocaine in humans. Drug Alcohol Depend. 82 (1), 19–24.
Nye, H.E., Nestler, E.J., 1996 Apr. Induction of chronic Fos-related antigens in rat brain by chronic morphine administration. Mol. Pharmacol. 49 (4), 636–645.
Pennypacker, K.R., Yang, X., Gordon, M.N., Benkovic, S., Miller, D., O'Callaghan, J.P., 2000. Long-term induction of Fos-related antigen-2 after methamphetamine-, methylenedioxymethamphetamine-, 1-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine- and trimethyltin-induced brain injury. Neuroscience 101 (4), 913–919.
Perrotti, L.I., Weaver, R.R., Robison, B., Renthal, W., Maze, I., Yazdani, S., Elmore, R.G., Knapp, D.J., Selley, D.E., Martin, B.R., Sim-Selley, L., Bachtell, R.K., Self, D.W., Nestler, E.J., 2008 May. Distinct patterns of DeltaFosB induction in brain by drugs of abuse. Synapse 62 (5), 358–369. https://doi.org/10.1002/syn.20500.
Piechota, M., Korostynski, M., Solecki, W., Gieryk, A., Slezak, M., Bilecki, W., Ziolkowska, B., Kostrzewa, E., Cymerman, I., Swiech, L., Jaworski, J., Przewlocki, R., 2010. The dissection of transcriptional modules regulated by various drugs of abuse in the mouse striatum. Genome Biol. 11 (5), R48. https://doi.org/10.1186/gb-2010-11-5-r48.
Pettit, H.O., Ettenberg, A., Bloom, F.E., Koob, G.F., 1984. Destruction of dopamine in the nucleus accumbens selectively attenuates cocaine but not heroin self-administration. Psychopharmacology 84, 167–173.
Raineri, M., Peskin, V., Goitia, B., Taravini, I.R., Giorgeri, S., Urbano, F.J., Bisagno, V., 2011 Oct. Attenuated methamphetamine induced neurotoxicity by modafinil administration in mice. Synapse 65 (10), 1087–1098. https://doi.org/10.1002/syn.20943.
Raineri, M., Gonzalez, B., Goitia, B., Garcia-Rill, E., Krasnova, I.N., Cadet, J.L., Urbano, F.J., Bisagno, V., 2012. Modafinil abrogates methamphetamine-induced neuroinflammation and apoptotic effects in the mouse striatum. PLoS One 7 (10), e46599. https://doi.org/10.1371/journal.pone.0046599.
Raineri, M., González, B., Rivero-Echeto, C., Muñiz, J.A., Gutiérrez, M.L., Ghanem, C.I., Cadet, J.L., García-Rill, E., Urbano, F.J., Bisagno, V., 2015 Jan. Differential effects of environment-induced changes in body temperature on modafinil's actions against methamphetamine-induced striatal toxicity in mice. Neurotox. Res. 27 (1), 71–83. https://doi.org/10.1007/s12640-014-9493-9.
Ribeiro, E.A., Scarpa, J.R., Garamszegi, S.P., Kasarskis, A., Mash, D.C., Nestler, E.J., 2017 Jul 14. Gene network dysregulation in dorsolateral prefrontal cortex neurons of humans with cocaine use disorder. Sci. Rep. 7 (1), 5412. https://doi.org/10.1038/s41598-017-05720-3.
Robinson, T.E., Kolb, B., 1999 Aug. Morphine alters the structure of neurons in the nucleus accumbens and neocortex of rats. Synapse 33 (2), 160–162.
Robison, A.J., Nestler, E.J., 2011 Oct 12. Transcriptional and epigenetic mechanisms of addiction. Nat. Rev. Neurosci. 12 (11), 623–637. https://doi.org/10.1038/nrn3111.
Rye, M., Sandve, G.K., Daub, C.O., Kawaji, H., Carninci, P., Forrest, A.R., Drabløs, F., 2014 Mar 26. FANTOM consortium. Chromatin states reveal functional associations for globally defined transcription start sites in four human cell lines. BMC Genomics 15, 120. https://doi.org/10.1186/1471-2164-15-120.
Saint-Preux, F., Bores, L.R., Tulloch, I., Ladenheim, B., Kim, R., Thanos, P.K., Volkow, N.D., Cadet, J.L., 2013 Jul 23. Chronic co-administration of nicotine and methamphetamine causes differential expression of immediate early genes in the dorsal striatum and nucleus accumbens of rats. Neuroscience 243, 89–96. https://doi.org/10.1016/j.neuroscience.2013.03.052.
Salzmann, J., Marie-Claire, C., Le Guen, S., Roques, B.P., Noble, F., 2003 Nov. Importance of ERK activation in behavioral and biochemical effects induced by MDMA in mice. Br. J. Pharmacol. 140 (5), 831–838.
Samaha, A.N., Mallet, N., Ferguson, S.M., Gonon, F., Robinson, T.E., 2004 Jul 14. The rate of cocaine administration alters gene regulation and behavioral plasticity: implications for addiction. J. Neurosci. 24 (28), 6362–6370.
Shilling, P.D., Kuczenski, R., Segal, D.S., Barrett, T.B., Kelsoe, J.R., 2006 Nov. Differential regulation of immediate-early gene expression in the prefrontal cortex of rats with a high vs low behavioral response to methamphetamine. Neuropsychopharmacology 31 (11), 2359–2367.
Shirayama, Y., Hashimoto, K., Iyo, M., Watanabe, K., Higuchi, T., Minabe, Y., 2000 Aug 25. 3,4-methylenedioxymethamphetamine (MDMA, ecstasy)-induced egr-1 mRNA in rat brain: pharmacological manipulation. Eur. J. Pharmacol. 402 (3), 215–222.
Shoda, T., Fukuda, K., Uga, H., Mima, H., Morikawa, H., 2001 Oct. Activation of mu-opioid receptor induces expression of c-fos and junB via mitogen-activated protein kinase cascade. Anesthesiology 95 (4), 983–989.
Solecki, W., Krowka, T., Kubik, J., Kaczmarek, L., Przewlocki, R., 2008 Jul 19. Role of fosB in behaviours related to morphine reward and spatial memory. Behav. Brain Res. 190 (2), 212–217. https://doi.org/10.1016/j.bbr.2008.02.040.
Spiegel, I., Mardinly, A.R., Gabel, H.W., Bazinet, J.E., Couch, C.H., Tzeng, C.P., Harmin, D.A., Greenberg, M.E., 2014 May 22. Npas4 regulates excitatory-inhibitory balance within neural circuits through cell-type-specific gene programs. Cell 157 (5), 1216–1229. https://doi.org/10.1016/j.cell.2014.03.058.
Steffensen, S.C., Stobbs, S.H., Colago, E.E., Lee, R.S., Koob, G.F., Gallegos, R.A., Henriksen, S.J., 2006 Nov. Contingent and non-contingent effects of heroin on mu-opioid receptor-containing ventral tegmental area GABA neurons. Exp. Neurol. 202 (1), 139–151.
Steward, O., Worley, P.F., 2001 Jun 19. A cellular mechanism for targeting newly synthesized mRNAs to synaptic sites on dendrites. Proc. Natl. Acad. Sci. U. S. A. 98 (13), 7062–7068.
Sulzer, D., Chen, T.K., Lau, Y.Y., Kristensen, H., Rayport, S., Ewing, A., 1995 May. Amphetamine redistributes dopamine from synaptic vesicles to the cytosol and promotes reverse transport. J. Neurosci. 15 (5 Pt 2), 4102–4108.
Sulzer, D., Cragg, S.J., Rice, M.E., 2016 Aug. Striatal dopamine neurotransmission: regulation of release and uptake. Basal Ganglia 6 (3), 123–148.
Sulzer, D., Rayport, S., 1990 Dec. Amphetamine and other psychostimulants reduce pH gradients in midbrain dopaminergic neurons and chromaffin granules: a mechanism of action. Neuron 5 (6), 797–808.
Sun, X., Lin, Y., 2016 Apr. Npas4: linking neuronal activity to memory. Trends Neurosci. 39 (4), 264–275. https://doi.org/10.1016/j.tins.2016.02.003.
Thiriet, N., Zwiller, J., Ali, S.F., 2001 Nov 16. Induction of the immediate early genes egr-1 and c-fos by methamphetamine in mouse brain. Brain Res. 919 (1), 31–40.
Thomsen, M., Hall, F.S., Uhl, G.R., Caine, S.B., 2009 Jan 28. Dramatically decreased cocaine self-administration in dopamine but not serotonin transporter knock-out mice. J. Neurosci. 29 (4), 1087–1092. https://doi.org/10.1523/JNEUROSCI.4037-08.2009.
Tomita, M., Katsuyama, H., Watanabe, Y., Shibaike, Y., Yoshinari, H., Tee, J.W., Iwachidou, N., Miyamoto, O., 2013. c-Fos immunoreactivity of neural cells in intoxication due to high-dose methamphetamine. J. Toxicol. Sci. 38 (5), 671–678.
Torres, O.V., McCoy, M.T., Ladenheim, B., Jayanthi, S., Brannock, C., Tulloch, I., Krasnova, I.N., Cadet, J.L., 2015 Aug 24. CAMKII-conditional deletion of histone deacetylase 2 potentiates acute methamphetamine-induced expression of immediate early genes in the mouse nucleus accumbens. Sci. Rep. 5, 13396. https://doi.org/10.1038/srep13396.
Unterwald, E.M., Rubenfeld, J.M., Kreek, M.J., 1994. Repeated cocaine administration upregulates kappa and mu, but not delta, opioid receptors. Neuroreport 5 (13), 1613–1616.
Vaughan, C.W., Ingram, S.L., Connor, M.A., Christie, M.J., 1997 Dec 11. How opioids inhibit GABA-mediated neurotransmission. Nature 390 (6660), 611–614.
Wade, C.L., Vendruscolo, L.F., Schlosburg, J.E., Hernandez, D.O., Koob, G.F., 2015 Jan. Compulsive-like responding for opioid analgesics in rats with extended access. Neuropsychopharmacology 40 (2), 421–428. https://doi.org/10.1038/npp.2014.188.
Wise, R.A., 2004 Jun. Dopamine, learning and motivation. Nat. Rev. Neurosci. 5 (6), 483–494.
Ye, L., Allen, W.E., Thompson, K.R., Tian, Q., Hsueh, B., Ramakrishnan, C., Wang, A.C., Jennings, J.H., Adhikari, A., Halpern, C.H., Witten, I.B., Barth, A.L., Luo, L., McNab, J.A., Deisseroth, K., 2016 Jun 16. Wiring and molecular features of prefrontal ensembles representing distinct experiences. Cell 165 (7), 1776–1788. https://doi.org/10.1016/j.cell.2016.05.010.
Zhang, D., Zhang, L., Lou, D.W., Nakabeppu, Y., Zhang, J., Xu, M., 2002. The dopamine D1 receptor, is a critical mediator for cocaine-induced, gene expression. J. Neurochem. 82 (6), 1453–1464.
Ziółkowska, B., Gieryk, A., Solecki, W., Przewłocki, R., 2015 Jan 22. Temporal and anatomic patterns of immediate-early gene expression in the forebrain of C57BL/6 and DBA/2 mice after morphine administration. Neuroscience 284, 107–124. https://doi.org/10.1016/j.neuroscience.2014.09.069.
Ziółkowska, B., Korostyński, M., Piechota, M., Kubik, J., Przewłocki, R., 2012. Effects of morphine on immediate-early gene expression in the striatum of C57BL/6J and DBA/2J mice. Pharmacol. Rep. 64 (5), 1091–1104.
Zubieta, J.K., Gorelick, D.A., Stauffer, R., Ravert, H.T., Dannals, R.F., Frost, J.J., 1996 Nov. Increased mu opioid receptor binding detected by PET in cocaine-dependent men is associated with cocaine craving. Nat. Med. 2 (11), 1225–1229.